REMARKS

The Office Action mailed February 18, 2010, was reviewed and the comments of the Patent and Trademark Office were considered. As of the last amendment, Claims 1-34 are pending and 24-27 and 30-34 were withdrawn from consideration. By this response, Claims 1, 3-4, 7-10, 16-18 and 21-22 are amended, Claims 2 and 20 are cancelled and new claims 35-39 are added. Support for the amendment can be found in the original claims and the specification generally.

The specification and claims have further been amended to correct a typographical error. The specification and claims as filed had a formula with [GH] group, and have been corrected to [HG]. Support can be found at page 16, l. 1, 12 and page 17 l. 5-10.

Further, Examiner states on page 4 of the Office Action that an English translation of the certified foreign priority paper was not provided. Applicants are filing the English translation herewith.

RESTRICTION

The Examiner maintained the prior restriction requirement, stating the claims lack unity of invention because the surfactant is option and thus the claims are anticipated by Huille *et al.* (corresponds to FR 2 786 098). The English language translation of FR 2 786 098 is US Patent 6,630,171. As noted below in some length under the 35 USC § 102 section, the currently amended claims cannot be anticipated by Huille because they share a technical feature not disclosed by Huille: submicronic particles of water-soluble biodegradable polymer (PO) carrying hydrophobic groups (HG) whereby the concentration of [PO] is such that $[PO] \geq 0.9.C1$, where C1 is the "*induced gelling*" concentration of the particles of PO, as measured in an IG test. Further, all claims require this limitation. As such, the claims share a "special technical feature" not found in the prior art. MPEP 1850. Applicant therefore respectfully requests the restriction requirement be withdrawn.

CLAIM OBJECTIONS

Claim 17 is objected for minor informalities. Applicant has amended claim 17 in order to correct this informality.

35 USC § 112 REJECTIONS

Claims 1, 2, 4-12, 16-23 and 28 are rejected under 35 USC § 112, second paragraph as being indefinite. The Examiner rejects claims 1, 2, 4-12, 16-23 and 28 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that claims 4, 7, 8, 10, 16, 17, 18, 21 and 22 are indefinite because preferences lead to confusion over the intended scope of the claim. The applicant amended these claims in order to overcome this issue and therefore respectfully requests the Examiner withdraws the rejection of these claims as being indefinite under 35 U.S.C. § 112, second paragraph.

DOUBLE PATENTING REJECTION

Claims 1-23, 28 and 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable on the ground of nonstatutory obviousness-type double patenting as being unpatentable over numerous co-pending Flamel applications. The cited references cannot be used to reject the claims because they have a later priority date than the instant application.

The instant application claims priority to FR 03/50886, and thus has a priority date of November 21, 2003. In contrast, the applications cited in the double patenting rejection have a priority date later than the instant application or the exact same priority date as the instant application. For instance, U.S. App. No. 10/580,035 has a priority date of November 21, 2003, U.S. App. No. 11/878,947 has a priority date of July 28, 2003, U.S. App. No. 10/580,023 has a priority date of November 21, 2003, U.S. App. No. 11,808,456 has a priority date of July 9, 2006, U.S. App. No. 11/658,803 has a priority date of July 30, 2004 and U.S. App. No. 12/003,095 has a priority date of December 20, 2006. As such, Applicants respectfully request the rejection be withdrawn.

The instant application is also rejected over claims 1-10, 15, 17-24 and 26 of the co-pending Application No. 10/516,733. Applicants note that the broadest claim in U.S. App. No. 10/516,733, claim 1, does not require i) submicronic particles of water-soluble biodegradable polymer (PO) carrying hydrophobic groups (HG) whereby the concentration of [PO] is such that [PO] ≥ 0.9.C1, where C1 is the "*induced gelling*" concentration of the particles of PO, as measured in an IG test. These are all limitations required by the broadest instant claims. As such, the current claims are patentably distinct from U.S. App. No. 10/516,733 and are not obvious. As such, Applicants respectfully request the rejection be withdrawn.

The instant application is also rejected over claims 1-23, 28 and 29 are rejected on the ground of nonstatutory obviousness type double patenting as being unpatentable over claims 1-21, 28-32 and 40 of U.S. Patent No. 6,630,171 ("Huille"). Applicants further note that the Examiner rejected certain claims under 35 U.S.C. § 102 and 103 over Huille. Applicants assert that the instant claims are patentably distinct from Huille and are not obvious for reasons stated below.

CLAIM REJECTIONS - 35 USC § 102

Claims 1, 6, 7, 16, 18,21 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Huille. "[R]ejections under 35 U.S.C. § 102 are proper only when the claimed subject matter is identically disclosed or described in the prior art." (emphasis and internal quotation marks omitted). *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972).

The main objective of the current invention is to find a formulation allowing an increased prolonged release time of the active ingredient, such that this release time is beyond 24h after administration *in vivo*. The applicant discovered that such objective could be met using a suspension of a polyaminoacid polymer PO, bearing hydrophobic groups attached laterally to the chain that must have a concentration of polymer PO greater than a critical concentration of 0.9 C1 corresponding to the formation of a gel in presence of BSA in an IG test (See specification at page 7, [0107]).

Huille does neither mention nor suggest the existence of a critical concentration above which the release time of the active ingredient is beyond 24 h after administration. Thus the key of the current invention is that the pharmaceutical composition must fulfill a non obvious

restrictive condition, namely that the concentration of polymer PO should be greater than a critical concentration of 0.9 C1.

This is also to the applicant's credit to have developed and fine-tuned an IG test that allows determining the value of the above mentioned concentration C1. More precisely, C1 is the concentration at which the formulation forms a gel *in vitro* without requiring a temperature or pH change, in presence of a specified concentration of BSA, namely 30mg/ml (See specification at page 7, [0107]).

This critical concentration is now defined in amended first claim:

> 1. Liquid pharmaceutical formulation for the prolonged release of interferon(s), this formulation comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer (PO) carrying hydrophobic groups (HG), said particles being non-covalently associated with at least one interferon, characterized in that:
>
> the dispersion medium of the suspension essentially consists of water,
>
> its concentration of [PO] is such that [PO] ≥ 0.9.C1, where C1 is the "induced gelling" concentration of the particles of PO, as measured in an IG test, making it possible to prolong and control the in vivo release time of the AP beyond 24 h after administration,
>
> it is liquid under the injection conditions,
>
> and it is also liquid at the physiological temperature and pH or in the presence of:
>
> a physiological electrolyte in a physiological concentration,
>
> or at least one surfactant.

In amended claim 1, the critical concentration 0.9 C1 at which the release time is significantly increased, the relation between this concentration 0.9 C1 and the *in vitro* protein-induced gelling phenomenon are totally new. These observations were not disclosed in the prior art Huille and have been discovered by the Applicant.

Thus amended independent claim 1 is not anticipated by Huille. Therefore, claims 6, 7, 16, 18, 21 and 28 depending from amended claim 1 are also not anticipated. For these reasons, the Applicants respectfully request that these rejections be withdrawn.

CLAIM REJECTIONS - 35 USC § 103

Rejection of Huille in view of Edwards

Claims 1, 5-8, 12-16, 18, 20-23 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huille in view of Edwards *et al.* (Arch. Dermatol., 1990, 126: 1029-1032, Abstract) ("Edwards").

The Examiner has rejected claims 1, 5-8, 12-16, 18, 20-23 and 28 under 35 U.S.C. § 103(a) as being obvious over Huille (U.S. Pat. 6,630,171) in view of Edwards *et al.* (Arch. Dermatol., 1990, 126 : 1029-1032, Abstract).

One of the major goals of this invention is to obtain a liquid pharmaceutical formulation that can delay the release of the interferon, without using temperature or pH change or organic solvent, that are potentially toxic in physiological medium. Here the interferon is advantageously non-denatured. Thus, its bioactivity remains complete.

Although Huille does not teach a viscosity of 5 Pa.s at 20°C, one of skill in the art would understand that a formulation having a viscosity below 5 Pa.s is liquid. This is moreover defined in the instant specification at page 11, ll 12-13. The limitation "of low viscosity" in claim 1 is only intended to reinforce the fact that the "liquid pharmaceutical formulation" is liquid and thus can be easily injected.

Edwards deals with a protamine zinc chelate interferon formulation. Edwards does not disclose the formation of a gel and even less a concentration of polymer that must be used in order to form a gel deposit *in vivo*.

Thus, neither Huille nor Edwards teaches or suggests the claimed limitation of a concentration of [PO] such that [PO] $\geq$ 0.9.C1. Huille and Edwards therefore do not render the instant claims obvious, and Applicants respectfully request the Examiner withdraw the rejection.

In addition, Applicants concur with the Examiner that Huille does not teach Formula IV (claim 8). *See*, Office Action at page 9. Examiner further asserted that there is no evidence on the record to show that HG arrangement of Formula (IV) gives unexpected property. Applicants note that the unexpected properties of the claimed structures comes from a concentration of [PO] such that [PO] $\geq$ 0.9.C1, not from the HG.

Rejection of Huille in view of Eliaz

Claims 1-4, 6, 7, 16, 18, 21, 28 and 29 are rejected as being unpatentable over of Huille in view of each Eliaz *et al.* (J. Biomed. Mater. Res., 2000, 50: 388-396) ("Eliaz").

As noted above, Huille does not teach or suggest the claimed limitation of a concentration of [PO] such that [PO] ≥ 0.9.C1. Neither does Eliaz.

Eliaz discloses a water-insoluble copolymer of polylactide-co-glycolide dissolved in a biocompatible water-miscible solvent. Upon intramuscular or subcutaneous injection into an aqueous environment, the biocompatible water-soluble solvent diffuses out of the polymer while water diffuses into the polymer matrix. Due to the polymer's insolubility in water, it coagulates or precipitates upon contact with water, thus resulting in a solid polymeric implant. *See* Eliaz at Introduction §3.

An aim of the instant invention is to ***avoid*** the use of a solvent to form a gel deposit *in vivo*. The main disadvantage of using a solvent is that this solvent can be "potentially denaturing for the [...] therapeutic proteins and toxic to the patient." Specification at page 3, ll. 14-15. For this reason, one of skill in the art would not combine Huille with Eliaz because the Eliaz solvent can denature the claimed interferon. Huille and Eliaz therefore do not render the instant claims obvious, and Applicants respectfully request the Examiner withdrawn the rejection.

Rejection of Huille in view of Regalado

Claims 1-4, 6, 7, 16, 18, 21, 28 and 29 are rejected as being unpatentable over of Huille in view of Regalado *et al.* (Macromolecules, 1999, 32:8580-8588, Applicant's IDS) ("Regalado")

At page 11, Point 14 of the Office Action, the Examiner seems to suggest that Regalado and Akiyoshi teach the "formation of gels *in vivo* contributes to the sustained release of encapsulated drugs". Applicants disagree and point out that none of these documents relates to *in vivo* studies and even less to encapsulated drugs.

Indeed, Regalado is directed to polymer chains consisting of water-soluble polyacrylamides hydrophobically modified with low-amounts of N,N-dihexylacrylamide. Regalado studies the viscoelasticity of polyacrylamide chains and shows that increasing the concentration of polyacrylamide leads to the formation of a three-dimensional network. It does

not disclose that a liquid suspension of polymer PO, such as disclosed in the current invention, can form a gel in the presence of 30 mg/ml of BSA and above a critical concentration C1 of polymer PO, according to an IG test as described in the specification at page 7, [0107]. Moreover, the claimed suspension must be compulsorily liquid to be easily injectable under the injection conditions and must become a gel only after injection. *See* specification at page 7, [0089] (stating "it is very important to note that these formulations are liquid, i.e. they advantageously have a very low viscosity, making them easy to inject. They only gel *in vivo*".)

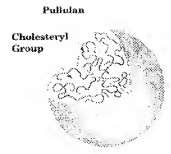
In Regalado, the formation of the gel *in vitro* leads to a polymer formulation having a viscosity too high to be easily injectable. Regalado is not concerned by the problem of injecting polymers to a patient. Furthermore, the type of polymer used by Regalado, which are telechelic associative polymers, must be avoided in the current invention because they are too viscous to be injectable. Moreover, Regalado does not mention a potential use of their polymers as a releasing device for pharmaceutical active ingredient and does even less disclose their affinity for an active ingredient such as the interferon for example. Thus a person skilled in the art would not have been prompted to use the teaching of Regalado to solve the problem of an injectable active ingredient release control. Huille and Regalado therefore do not render the instant claims obvious, and Applicants respectfully request the Examiner withdraw the rejection.

Rejection of Huille in view of Akiyoshi

Claims 1-4, 6, 7, 16, 18, 21, 28 and 29 are rejected as being unpatentable over of Huille in view of Akiyoshi *et al.* (Macromolecules, 1997, 30: 857-861) ("Akiyoshi").

As noted above, Applicants disagree with the Examiner that Akiyoshi teaches "formation of gels *in vivo* contributes to the sustained release of encapsulated drugs". *See* Office Action at 11. Applicants assert that Akiyoshi does not relate to *in vivo* studies much less encapsulated drugs.

Akiyoshi is directed to nanoparticles which are suspended in water. *See* Akiyoshi at page 860, illustrating the figure below.



Akiyoshi relates to a hydrogel nanoparticle of a hydrophobized polysaccharide, pullulans. Akiyoshi studies self-assembly of amphiphilic molecules to develop new strategy in chemical synthesis, with the potential of generating non biological structures with dimensions of 20 to 30 nanometers. Akiyoshi does not disclose how a liquid suspension of polymer PO such as in the current invention can form a gel in the presence of 30 mg/ml of BSA, above a critical concentration C1 of polymer PO, according to an IG test as described in the specification at page 7, [0107].

Akiyoshi mentions that one bovine serum albumin can complex with one CHP self-aggregate in water (page 857, col 1, last two lines, col 2, first two lines), thus increasing the stability of the bovine serum albumin. However, Akiyoshi does not teach that a polymer suspension leads to the formation of a gel in the presence of a sufficient amount of BSA and a determined concentration of polymer in order to achieve the IG test as described in the instant application. Thus a person skilled in the art would have found no indication in Akiyoshi regarding the formation of a gel in the presence of BSA as required in the instant first claim.

At page 12, Point 14 of the Office Action, the examiner further asserts that "Huille *et al.* teach suspending their particles in aqueous solutions comprising BSA (Example 7)". Huille at Example 7, however, does not teach suspending particles in an aqueous solution because the particles used in this example are already suspended before diluting "in increasing volumes of an isotonic 0.5% bovine serum albumin solution". Moreover, the skilled person knows that 0.5% BSA is used in a routine dissociation test such as described in Example 7. As explained in this example, the fraction of active principle released from the polymer particles during the dissociation test increases with the dilution, *i.e.* with the amount of BSA solution added to the particles suspension. A skilled person who would proceed to the dissociation test according to Huille at Example 7 would not observe any gelling of the polymer *in vitro* because of the

following reasons: **1)** the concentration of BSA used in the dissociation test of Example 7 is 0.5%, i.e. 5 mg/ml, which is not sufficient to achieve the IG test requiring a BSA concentration of 30 mg/ml (see at page 13, ll 7-9); **2)** the diluted PO solutions have a concentration below C1 (the concentration before dilution being 56 mg/ml, this concentration can only decrease until dilution 20); **3)** the beginning of the formation of a gel can only be observed when using a specific and sophisticated apparatus (See [0108]). Therefore, the skilled person who would proceed to the dissociation test according to Huille at Example 7 would not observe any gelling of the polymer *in vitro*.

For at least these reasons, Huille and Akiyoshi do not render the instant claims obvious, and Applicants respectfully request the Examiner withdraw the rejection.

Rejection of Huille in view of Kim and Seo

The Examiner first states that claims 1, 6, 7, 16-19, 21, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huille *et al.* in view of both Kim et al. (U.S. Patent No. 5,869,703) ("Kim") and Seo *et al.* (U.S. Patent No. 7,311,901) ("Seo"), but only addresses obviousness of claims 17 and 19.

As noted above, Huille does not teach or suggest the claimed limitation of a concentration of [PO] such that [PO] $\geq$ 0.9.C1. Kim and Seo also do not teach this limitation. As such, the references do not render the instant claims obvious, and Applicants respectfully request the Examiner withdraw the rejection.

Rejection of Huille in view of Conover

Claims 1, 6, 7, 9-11, 16, 18, 21, and 28 are rejected under 35 U.S.C.103(a) as being unpatentable over Huille *et al.* in view of Conover *et al.* (Anti-Cancer drug Design, 1999, 14:499-506) ("Conover").

As noted above, Huille does not teach or suggest the claimed limitation of a concentration of [PO] such that [PO] $\geq$ 0.9.C1. Conover also does not teach this limitation. As such, the references do not render the instant claims obvious, and Applicants respectfully request the Examiner withdraw the rejection.

CONCLUSION

In view of the above remarks and amendments, the Applicants respectfully submit that each of the pending objections and rejections has been addressed and overcome, placing all of the claims of the present application in condition for allowance. If the Examiner believes that personal communication will expedite prosecution of this application, or should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number provided below.

Applicants believe no fee is due with this submission. If a fee is due, however, the U.S. Patent and Trademark Office is authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, under Order No. 022290. 0160PTUS from which the undersigned is authorized to draw.

Dated: May 18, 2010

Respectfully submitted,

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Attachment:
Certification of Verification for French Application No. 03 50886
Verified English Translation of French Application No. 03 50886